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








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**Proteasome Degradation of GRK2 During Ischemia and Ventricular Tachyarrhythmias in a Canine Model of Myocardial Infarction.**  
Am J Physiol Heart Circ Physiol. 2005 Jul 1; [Epub ahead of print]  
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- ☐ 2: [Kochi Y, Yamada R, Suzuki A, Harley JB, Shirasawa S, Sawada T, Bae SC, Tokuhito S, Chang X, Sekine A, Takahashi A, Tsunoda T, Ohnishi Y, Kaufman KM, Kang CP, Kang C, Otsubo S, Yumura W, Mimori A, Koike T, Nakamura Y, Sasazuki T, Yamamoto K.](#) Related Articles, Links  
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- ☐ 3: [McClain MT, Lutz CS, Kaufman KM, Faig OZ, Gross TF, James JA.](#) Related Articles, Links  
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- ☐ 6: [Kaufman KM, Rankin J, Harley IT, Kelly JA, Harley JB, Scofield RH.](#) Related Articles, Links  
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-  **7:** [Edberg JC, Langefeld CD, Wu J, Moser KL, Kaufman KM, Kelly J, Bansal V, Brown WM, Salmon JE, Rich SS, Harley JB, Kimberly RP.](#) [Related Articles, Links](#)  
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**Pellet pestle homogenization of agarose gel slices at 45 degrees C for deoxyribonucleic acid extraction.**  
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-  **10:** [Kaufman KM, Kirby MY, McClain MT, Harley JB, James JA.](#) [Related Articles, Links](#)  
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-  **11:** [Kaufman KM, Kelly J, Gray-McGuire C, Asundi N, Yu H, Reid J, Baird T, Hutchings D, Bruner G, Scofield RH, Moser K, Harley JB.](#) [Related Articles, Links](#)  
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-  **12:** [Kaufman KM, Farris AD, Gross JK, Kirby MY, Harley JB.](#) [Related Articles, Links](#)  
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-  **13:** [Lee LA, Walsh P, Prater CA, Su LJ, Marchbank A, Egbert TB, Dellavalle RP, Targoff IN, Kaufman KM, Chorzelski TP, Jablonska S.](#) [Related Articles, Links](#)  
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-  **14:** [Glass KA, Kaufman KM, Smith AL, Johnson EA, Chen JH, Hotchkiss J.](#) [Related Articles, Links](#)  
**Toxin production by Clostridium botulinum in pasteurized milk treated with carbon dioxide.**  
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-  Immunization of mice with human 60-kd Ro peptides results in epitope spreading if the peptides are highly homologous between human and mouse.  
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-  Survival of bacterial pathogens in pasteurized process cheese slices stored at 30 degrees C.  
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- ☐ **17:** [Schreck SF, Plumb ME, Platteborze PL, Kaufman KM, Michelotti GA, Letson CS, Sodetz JM.](#) [Related Articles](#), [Links](#)
-  Expression and characterization of recombinant subunits of human complement component C8: further analysis of the function of C8 alpha and C8 gamma.  
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- ☐ **18:** [James JA, Kaufman KM, Farris AD, Taylor-Albert E, Lehman TJ, Harley JB.](#) [Related Articles](#), [Links](#)
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<input type="checkbox"/>	L14	LMP-2B	0
<input type="checkbox"/>	L13	LMP-2A	0
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<input type="checkbox"/>	L11	LMP-1	5
<input type="checkbox"/>	L10	EBNA and latent protein	0

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L1 ANSWER 1 OF 10 MEDLINE on STN  
AN 2004640931 IN-PROCESS  
DN PubMed ID: 15617340  
TI Recombinant AAV-LMP-induced LMP specific cytotoxic response to autologous lymphoblastoid cell lines tranformed by Epstein-Barr virus.  
AU Zhao F; Liu H; Zhou L; Cai W; Du B; Ye S; Zeng Y  
CS Institute of Virology, Chinese Academy of Preventive Medicine, Beijing 100052.  
SO Zhonghua shi yan he lin chuang bing du xue za zhi = Zhonghua shiyan he linchuang bingduxue zazhi = Chinese journal of experimental and clinical virology, (1997 Sep) 11 (3) 247-51.  
Journal code: 9602873. ISSN: 1003-9279.  
CY China  
DT Journal; Article; (JOURNAL ARTICLE)  
LA Chinese  
FS NONMEDLINE; IN-PROCESS; NONINDEXED; Priority Journals  
ED Entered STN: 20041225  
Last Updated on STN: 20041225

L1 ANSWER 2 OF 10 MEDLINE on STN  
AN 2003296860 MEDLINE  
DN PubMed ID: 12825212  
TI Treatment of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis (EBV-HLH) in young adults: a report from the HLH study center.  
AU Imashuku Shinsaku; Kuriyama Kikuko; Sakai Rika; Nakao Yoshitaka; Masuda Shin-ichi; Yasuda Norimasa; Kawano Fumio; Yakushijin Kimikazu; Miyagawa Akiko; Nakao Taisei; Teramura Tomoko; Tabata Yasuhiro; Morimoto Akira; Hibi Shigeyoshi  
CS Kyoto City Institute of Health and Environmental Sciences, Kyoto, Japan.. shinim95@mbx.kyoto-inet.or.jp  
SO Medical and pediatric oncology, (2003 Aug) 41 (2) 103-9.  
Journal code: 7506654. ISSN: 0098-1532.  
CY United States  
DT (EVALUATION STUDIES)  
Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 200308  
ED Entered STN: 20030626  
Last Updated on STN: 20030813  
Entered Medline: 20030812

L1 ANSWER 3 OF 10 MEDLINE on STN  
AN 2003120615 MEDLINE  
DN PubMed ID: 12634387  
TI The B subunit of Escherichia coli heat-labile enterotoxin enhances CD8+ cytotoxic-T-lymphocyte killing of Epstein-Barr virus-infected cell lines.  
AU Ong Kong-Wee; Wilson A Douglas; Hirst Timothy R; Morgan Andrew J  
CS Department of Pathology and Microbiology, School of Medical Sciences, University of Bristol, United Kingdom.  
SO Journal of virology, (2003 Apr) 77 (7) 4298-305.  
Journal code: 0113724. ISSN: 0022-538X.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 200304  
ED Entered STN: 20030314  
Last Updated on STN: 20030426  
Entered Medline: 20030425

L1 ANSWER 4 OF 10 MEDLINE on STN  
AN 2002641258 MEDLINE  
DN PubMed ID: 12400609  
TI Antigen presenting cells transfected with LMP2a RNA induce CD4+

LMP2a-specific cytotoxic T lymphocytes which kill via a Fas-independent mechanism.

AU Su Zhen; Peluso Mario V; Raffegerst Silke H; Schendel Dolores J; Roskrow Marie A

CS Medizinische Klinik III, Ludwigs-Maximilians-Universitat and Institut fur Molekulare Immunologie, GSF National Research Centre for Environment and Health, Munchen, Germany.

SO Leukemia & lymphoma, (2002 Aug) 43 (8) 1651-62.  
Journal code: 9007422. ISSN: 1042-8194.

CY England: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200303

ED Entered STN: 20021029  
Last Updated on STN: 20030313  
Entered Medline: 20030312

L1 ANSWER 5 OF 10 MEDLINE on STN

AN 2001470494 MEDLINE

DN PubMed ID: 11493400

TI Epstein--Barr virus post-transplant lymphoproliferative disease and virus-specific therapy: pharmacological re-activation of viral target genes with arginine butyrate.

AU Mentzer S J; Perrine S P; Faller D V

CS Division of Thoracic Surgery, Department of Surgery, Brigham and Women's Hospital, and the Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts 02115, USA.. smentzer@partners.org

NC CA85687 (NCI)

SO Transplant infectious disease : an official journal of the Transplantation Society, (2001 Sep) 3 (3) 177-85. Ref: 91  
Journal code: 100883688. ISSN: 1398-2273.

CY Sweden

DT Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)

LA English

FS Priority Journals

EM 200110

ED Entered STN: 20010823  
Last Updated on STN: 20011022  
Entered Medline: 20011018

L1 ANSWER 6 OF 10 MEDLINE on STN

AN 2000507970 MEDLINE

DN PubMed ID: 11059774

TI Activation of lytic Epstein-Barr virus (EBV) infection by radiation and sodium butyrate in vitro and in vivo: a potential method for **treating** EBV-positive malignancies.

AU Westphal E M; Blackstock W; Feng W; Israel B; Kenney S C

CS University of North Carolina Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, 27599-7295, USA.

NC R01 CA 66519 (NCI)

SO Cancer research, (2000 Oct 15) 60 (20) 5781-8.  
Journal code: 2984705R. ISSN: 0008-5472.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200011

ED Entered STN: 20010322  
Last Updated on STN: 20010322  
Entered Medline: 20001108

L1 ANSWER 7 OF 10 MEDLINE on STN

AN 2000141830 MEDLINE

DN PubMed ID: 10678362

TI The nitroreductase/CB1954 combination in Epstein-Barr virus-positive

B-cell lines: induction of bystander killing in vitro and in vivo.  
 AU Westphal E M; Ge J; Catchpole J R; Ford M; Kenney S C  
 CS Lineberger Comprehensive Cancer Center, University of North Carolina,  
 Chapel Hill 27599-7295, USA.  
 NC R01 CA 66519 (NCI)  
 SO Cancer gene therapy, (2000 Jan) 7 (1) 97-106.  
 Journal code: 9432230. ISSN: 0929-1903.  
 CY ENGLAND: United Kingdom  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 200002  
 ED Entered STN: 20000314  
 Last Updated on STN: 20000314  
 Entered Medline: 20000229

L1 ANSWER 8 OF 10 MEDLINE on STN  
 AN 1999211475 MEDLINE  
 DN PubMed ID: 10197618  
 TI Induction of lytic Epstein-Barr virus (EBV) infection in EBV-associated malignancies using adenovirus vectors in vitro and in vivo.  
 AU Westphal E M; Mauser A; Swenson J; Davis M G; Talarico C L; Kenney S C  
 CS UNC Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, 27599, USA.  
 NC P01-CA19014 (NCI)  
 R01 CA 66519 (NCI)  
 SO Cancer research, (1999 Apr 1) 59 (7) 1485-91.  
 Journal code: 2984705R. ISSN: 0008-5472.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals; AIDS  
 EM 199904  
 ED Entered STN: 19990504  
 Last Updated on STN: 19990504  
 Entered Medline: 19990421

L1 ANSWER 9 OF 10 MEDLINE on STN  
 AN 97368336 MEDLINE  
 DN PubMed ID: 9223331  
 TI Growth arrest of Epstein-Barr virus immortalized B lymphocytes by adenovirus-delivered ribozymes.  
 AU Huang S; Stupack D; Mathias P; Wang Y; Nemerow G  
 CS Department of Immunology, IMM-19, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA.  
 NC 2MO1 RR0833 (NCRR)  
 CA36204 (NCI)  
 HL54352 (NHLBI)  
 SO Proceedings of the National Academy of Sciences of the United States of America, (1997 Jul 22) 94 (15) 8156-61.  
 Journal code: 7505876. ISSN: 0027-8424.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199708  
 ED Entered STN: 19970908  
 Last Updated on STN: 19970908  
 Entered Medline: 19970827

L1 ANSWER 10 OF 10 MEDLINE on STN  
 AN 97240777 MEDLINE  
 DN PubMed ID: 9120290  
 TI Conserved CTL epitopes within EBV latent membrane protein 2: a potential target for CTL-based tumor therapy.  
 AU Lee S P; Tierney R J; Thomas W A; Brooks J M; Rickinson A B  
 CS Institute for Cancer Studies, Medical School, University of Birmingham, United Kingdom.



SO Journal of immunology (Baltimore, Md. : 1950), (1997 Apr 1) 158 (7)  
3325-34.  
Journal code: 2985117R. ISSN: 0022-1767.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Abridged Index Medicus Journals; Priority Journals  
EM 199704  
ED Entered STN: 19970506  
Last Updated on STN: 19980206  
Entered Medline: 19970424

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L1 ANSWER 1 OF 10 MEDLINE on STN

AB Epstein-Barr virus is believed to be controlled in normal host by virus specific cytotoxic T lymphocytes (CTL). Although unable to eliminate EBV from the body, CTL seems to be essential in control of latently infected cells. Infusion of autologous EBV specific CTL, which can be produced in laboratory by separating lymphocytes from patients and stimulating them with EBV antigen, will provide an effective method of preventing and **treating** EBV-related diseases. We inserted the LMP gene of EB virus into an AAV vector pACP and packed it in Ad2 infected 293 cells by co-transfecting with plasmid Ad8, which produced the recombinant virus rAAV-LMP. The recombinant virus was used to infect stimulating cells and LMP antigen was expressed on the surface of these cells. Then the stimulating cells were irradiated and co-cultured with T lymphocytes. The EBV specific CTLs were obtained. The target cells were autologous LCLs from EBV-transformed B lymphocytes. The CTL activity was assayed by BLT activity method. The result indicated that all the four CTL strains could recognize and kill their target cells. This study has laid the technical basis for us to prevent and treat nasopharyngeal carcinoma in China with molecular biological methods.

L1 ANSWER 2 OF 10 MEDLINE on STN

AB BACKGROUND: Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis (EBV-HLH), also known as EBV-associated hemophagocytic syndrome, develops mostly in children and young adults and may be fatal. Early etoposide treatment has been confirmed to be effective in children. However, it is unclear whether the same treatment is useful in adults. PROCEDURE: To assess whether etoposide is effective in treating young adult cases, we retrospectively studied the therapeutic measures taken and outcomes in 20 young adult cases of EBV-HLH. Eleven cases were registered in our HLH study center in Kyoto and nine derived from the literature. The patients were between 17 and 33 years old and eight were males. The influence of gender, cell lineage (T- or natural killer-), EBV serology pattern, jaundice and treatment on the outcome was assessed. RESULTS AND CONCLUSIONS: Patients receiving etoposide within four weeks after diagnosis had a good prognosis as five of the seven patients survived compared to one of 13 not treated with etoposide or treated late (chi-square test for survival,  $P = 0.0095$ ). The Kaplan-Meier analysis showed the 2.5-year survival of  $85.7 \pm 13.2\%$  in the early etoposide-treated patients, compared to  $10.3 \pm 9.4\%$  in the remaining patients (log-rank test,  $P = 0.0141$ ). Thus, early etoposide treatment is effective in **treating** EBV-HLH in young adults as well as in children.  
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L1 ANSWER 3 OF 10 MEDLINE on STN

AB Epstein-Barr virus (EBV) is associated with a number of important human cancers, including nasopharyngeal carcinoma, gastric carcinoma, and Hodgkin's lymphoma. These tumors express a viral nuclear antigen, EBV nuclear antigen 1 (EBNA1), which cannot be presented to T cells in a major histocompatibility complex class I context, and the viral latent membrane proteins (LMPs). Although the LMPs are expressed in these tumors, no effective immune response is made. We report here that exposure to the cholera-like enterotoxin B subunit (EtxB) in EBV-infected lymphoblastoid

cell lines (LCLs) enhances their susceptibility to killing by LMP-specific CD8(+) cytotoxic T lymphocytes (CTLs) in a HLA class I-restricted manner. CTL killing of LCLs is dramatically increased through both transporter-associated protein-dependent and -independent epitopes after EtxB treatment. The use of mutant B subunits revealed that the enhanced susceptibility of LCLs to CTL killing is dependent on the B subunit's interaction with GM(1) but not its signaling properties. These important findings could underpin the development of novel approaches to **treating** EBV-associated malignancies and may offer a general approach to increasing the presentation of other tumor and viral antigens.

L1 ANSWER 4 OF 10 MEDLINE on STN

AB Recent reports have demonstrated that EBV can be used as a target of specific CTL-based treatments in severe chronic EBV, immunoblastic B cell lymphoma and Hodgkin's disease (HD). Based upon the promising results from these in vivo studies, it has been suggested that an antigen-specific CTL-based immunotherapy may be of benefit in **treating** EBV-associated tumors such as HD and nasopharyngeal carcinoma (NPC) which express the potentially immunogenic antigens, LMP1 and LMP2a. Recent work from our group has demonstrated that LMP2a-specific CTLs may be generated in vitro using autologous antigen presenting cells which have been transfected with polyadenylated LMP2a RNA in the presence of a cationic lipid. In this study, we demonstrate that the presence of the lipid enhances dendritic cell (DC) transfection efficiency and appears to protect the intracellular LMP2a RNA from degradation by cellular RNases. Significantly, these improvements resulted in the transfected DCs having a superior ability to stimulate autologous T cell proliferation. These LMP2a + DCs were used to stimulate LMP2a-specific effector cells which were predominantly a mixture of cytotoxic and helper CD4+ T cells. The molecular mechanisms whereby these CD4+ T cells lyzed their LMP2a-expressing targets was investigated and we show that, although expressing Fas ligand on their surface, LMP2a-specific CD4+ effector cells kill their targets using the Ca<sup>2+</sup>-dependent perforin/granzyme pathway which is the same mechanism used by CD8+ CTLs.

L1 ANSWER 5 OF 10 MEDLINE on STN

AB Lymphoproliferative disorders associated with the Epstein-Barr virus (EBV) include non-Hodgkin's lymphoma, Hodgkin's lymphoma, and "post-transplant lymphoproliferative disorders" (PTLD), which occur with immunosuppression after marrow and organ transplantation. PTLD is characterized by actively proliferating, latently infected EBV(+) B-lymphocytes, and often manifests a rapidly progressive fatal clinical course if the immunosuppression cannot be reversed. Lung transplant recipients are a subset of patients at special risk for developing PTLD. The incidence of PTLD development in these patients has been estimated at 5--10%. Whereas immunologic and antiviral therapy have been moderately effective for **treating** EBV-associated infections in the lytic phase, they have been less useful in the more common latent phase of the disease. One common treatment for herpesvirus infections has targeted the virus-specific enzyme thymidine kinase (TK). The lack of viral TK expression in EBV(+) tumor cells, due to viral latency, makes anti-viral therapy alone ineffective as an anti-neoplastic therapy, however. We have developed a strategy for the treatment of EBV-associated lymphomas/PTLD using pharmacologic induction of the latent viral TK gene and enzyme in the tumor cells, followed by treatment with ganciclovir. Arginine butyrate selectively activates the EBV TK gene in latently EBV-infected human lymphoid cells and tumor cells. A Phase I/II trial has been initiated, employing an intra-patient dose escalation of arginine butyrate combined with ganciclovir. In six patients with EBV-associated lymphomas or PTLD, all of which were resistant to conventional radiation and/or chemotherapy, this combination produced complete clinical responses in four of six patients, with a partial response occurring in a fifth patient. Pathologic examination in two of three patients demonstrated complete necrosis of the EBV lymphoma, with no residual disease, following a single three-week course of the combination therapy. Possible side-effects of the therapy included nausea and reversible lethargy at the highest doses. One patient suffered acute liver failure, thought to be secondary to

release of FasL from the necrotic tumor. Analysis of patient-derived tumor cells in culture demonstrated that arginine butyrate produced selective induction of the EBV TK gene, which then conferred sensitivity to ganciclovir, resulting in tumor apoptosis. Additional patient accrual is sought for further evaluation of this therapy.

L1 ANSWER 6 OF 10 MEDLINE on STN

AB The consistent presence of the EBV genome in certain tumors offers the potential for novel EBV-directed therapies. Switching the latent form of EBV infection present in most EBV-positive tumor cells into the cytolytic form may be clinically useful because lytic EBV infection leads to host cell destruction, and very few normal cells contain the EBV genome. It would also be therapeutically advantageous to induce expression of EBV-encoded lytic proteins that convert the nucleoside analogues ganciclovir (GCV) and 3'-azido-3'-deoxythymidine (AZT) into their active, cytotoxic forms. In this report, we have explored two different approaches for activating the lytic form of EBV infection in tumors. We show that gamma-irradiation at clinically relevant doses induces lytic EBV infection in lymphoblastoid cell lines in vitro as well as in EBV-positive B-cell tumors in SCID mice. In addition, sodium butyrate (given as a single i.p. dose) is effective for activating lytic viral infection in some EBV tumor types in SCID mice. We also examined whether low-dose gamma-irradiation treatment of EBV-positive lymphoblastoid cells in vitro promotes GCV or AZT susceptibility. The combination of radiation with either GCV or AZT induced significantly more cell killing in vitro than either radiation or prodrug treatment alone. Most importantly, we found that the combination of gamma-irradiation and GCV was much more effective in **treating** EBV-positive lymphoblastoid tumors in SCID mice than either agent alone. Thus, GCV or AZT treatment could potentially enhance the therapeutic efficacy of radiation therapy for EBV-positive lymphomas in patients.

L1 ANSWER 7 OF 10 MEDLINE on STN

AB Epstein-Barr virus (EBV)-based gene delivery vectors that preferentially express toxic genes in EBV-infected cells could be used to target EBV-positive tumors for destruction. We have shown previously that the cytosine deaminase (CD) enzyme, which converts the prodrug 5-fluorocytosine (5-FC) into the toxic compound 5-fluorouracil efficiently kills EBV-positive cells in the presence of 5-FC, with a substantial bystander killing effect in vitro and in vivo. To identify the optimal enzyme/prodrug combination for **treating** EBV-positive lymphomas, we have compared the effectiveness of the CD/5-FC combination with the nitroreductase (NTR)/CB1954 combination for killing EBV-positive B-cell lines. NTR metabolizes CB1954 into an alkylating agent that cross-links DNA. When the CD gene or the NTR gene were transfected into two different EBV-positive B-cell lines in vitro, approximately 90% of cells were killed in a prodrug-dependent manner, although the transfection efficiency was <5%. However, severe combined immunodeficient mouse tumors containing either 30% or 100% of NTR-expressing Burkitt lymphoma (Jijoye) cells were growth inhibited, but not cured, by treatment with intraperitoneal CB1954 (20 mg/kg/day) for 10 days. These results suggest that the NTR/CB1954 combination induces efficient bystander killing of EBV-positive B-cell lines in vitro but may not be as effective as the CD/5-FC combination for treating B-cell lymphomas in vivo.

L1 ANSWER 8 OF 10 MEDLINE on STN

AB The consistent presence of EBV genomes in certain tumor types (in particular, AIDS-related central nervous system lymphomas and nasopharyngeal carcinomas) may allow novel, EBV-based targeting strategies. Tumors contain the latent (transforming) form of EBV infection. However, expression of either of the EBV immediate-early proteins, BZLF1 and BRLF1, is sufficient to induce lytic EBV infection, resulting in death of the host cell. We have constructed replication-deficient adenovirus vectors expressing the BZLF1 or BRLF1 immediate-early genes and examined their utility for killing latently infected lymphoma cells in vitro and in vivo. We show that both the BZLF1 and BRLF1 vectors efficiently induce lytic EBV infection in Jijoye cells (an EBV-positive Burkitt lymphoma cell line). Furthermore, lytic EBV

infection converts the antiviral drug, ganciclovir (GCV), into a toxic (phosphorylated) form, which inhibits cellular as well as viral DNA polymerase. When Jijoye cells are infected with the BZLF1 or BRLF1 adenovirus vectors in the presence of GCV, viral reactivation is induced, but virus replication is inhibited (thus preventing the release of infectious EBV particles); yet cells are still efficiently killed. Finally, we demonstrate that the BZLF1 and BRLF1 adenovirus vectors induce lytic EBV infection when they are directly inoculated into Jijoye cell tumors grown in severe combined immunodeficiency mice. These results suggest that induction of lytic EBV infection in tumors, in combination with GCV, may be an effective strategy for **treating EBV**-associated malignancies.

L1 ANSWER 9 OF 10 MEDLINE on STN  
AB Epstein-Barr virus (EBV) infection is associated with several human diseases that involve unrestricted proliferation of B lymphocytes. EBV nuclear antigen 1 (EBNA-1) is expressed in all EBV-infected cells and plays an essential role in persistence of the EBV genome. EBNA-1 has also been reported to have oncogenic potential. As an approach for **treating EBV** infections, we examined the capacity of EBNA-1 ribozymes delivered by recombinant adenoviruses to suppress EBNA-1 expression and to block virus-induced B cell proliferation. In contrast to primary B cells, EBV-transformed B lymphoblastoid cell lines expressed alphav integrins, the adenovirus internalization receptors, and were also susceptible to adenovirus-mediated gene delivery. Adenovirus delivery of a specific ribozyme (RZ1) to lymphoblastoid cell lines, suppressed EBNA-1 mRNA and protein expression, significantly reduced the number of EBV genomes, and nearly abolished cell proliferation in low serum. Adenovirus delivery of RZ1 also prevented EBV infection of an established EBV-negative B cell line. These studies demonstrate the potential use of adenovirus-encoded ribozymes to treat EBV-induced lymphoproliferative disorders.

L1 ANSWER 10 OF 10 MEDLINE on STN  
AB In healthy virus carriers, EBV is subject to strong CTL responses that principally target the EBV nuclear Ag (EBNA) 3A, 3B, 3C subset of virus proteins. In vitro-reactivated CTLs of this kind have proved very effective in **treating EBV**-positive immunoblastic lymphoma, a malignancy that expresses the full range of virus proteins. However, targeting other EBV-positive tumors will require CTLs that recognize some of the subdominant viral Ags since in nasopharyngeal carcinoma and EBV-positive Hodgkin's disease, EBNA1, latent membrane protein (LMP) 1, and LMP2 are the only virus proteins present. Studying healthy virus carriers (Caucasian and Chinese), we identified five CTL target epitopes in LMP2 restricted through HLA alleles particularly common in the southern Chinese population, which is most at risk for nasopharyngeal carcinoma (HLA-A2, 50%; A11, 50%; A24, 30%; and B40, 32%). Furthermore, we analyzed the effect of HLA subtype polymorphism, especially in the context of A2 for which four subtypes are present at significant frequency in the Chinese population. As to virus polymorphism, LMP2 epitope sequences (in contrast to EBNA 3A, 3B, and 3C epitopes) were shown to be antigenically conserved among EBV isolates from different world populations, including viruses present in nasopharyngeal carcinoma and Hodgkin's disease biopsy samples. Thus, nasopharyngeal carcinoma and Hodgkin's disease are predicted to express LMP2 proteins that contain conserved CTL target epitopes restricted through common HLA alleles; boosting responses to these epitopes could form the basis of a CTL-based therapy for these malignancies.

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L1 10 S TREATING EBV  
L2 0 S TREATING EBVNA